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PHENOXYALIPHATIC ACIDS AND THEIR DERIVATIVES

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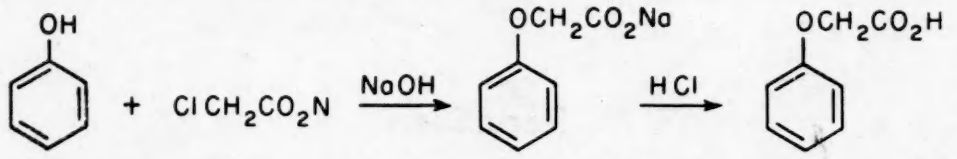
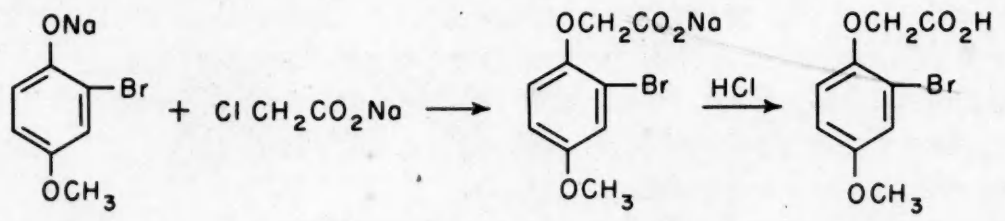
Phenoxyaliphatic acids, because of their use as plant-growth regulators and weed killers, have long been the subject of wide investigation. With the introduction of 2,4-dichlorophenoxyacetic acid (2,4D) as a derivative possessing great phytohormone activity, an intensive program of investigation was undertaken to expand the knowledge of this series of compounds. Prior to this discovery in the 1940's, many articles dating as far back as 1874 had been written on the preparation, properties, and reactions of these compounds. The studies of Fritsche (1), Hayes and Branch (2), Jacobs and Heidelberger (3), and Synerholm and Zimmerman (4) proved fruitful in bringing forth useful information concerning this increasingly important topic.

Preparation

Various methods can be used to prepare phenoxyaliphatic acids. These are generally variations of the condensation of a phenol with a chloro- or bromoaliphatic acid in the presence of alkali. This method is used chiefly in preparing the more simple



derivatives of phenoxyacetic acid. Many variations were conceived to control the rate of reaction. The use of sodium salts seems to reduce the rate, as, for example, the reaction of sodium *p*-ethoxyphenoxide with sodium chloroacetate to yield, after acidification, *p*-ethoxyphenoxyacetic acid. Another example of this method is shown in the preparation of (2-bromo-4-methoxyphenoxy)acetic acid. Nametkin, Bokarev,



and Mel'nikov (5) used this method to prepare about forty different alkoxy halogen derivatives.

Often, the preparation of a phenoxy acid proceeds better when prepared through the ester, followed by hydrolysis to the free acid (4). The esters, being liquids, are

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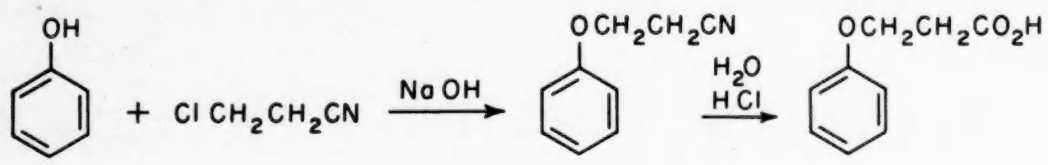
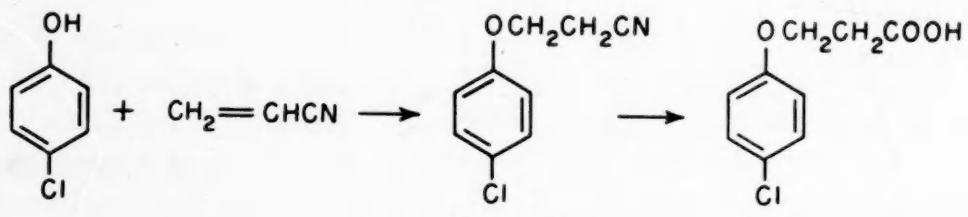
easily purified by distillation, allowing the subsequent hydrolysis, uninhibited by impurities. Phenoxyalkylacetic acids are frequently made in this way.

Phenoxypropionic acids can have the phenoxy group on either the α or the β carbon atom. When it is on the α, the acid is phenoxymethylacetic acid of the class just mentioned. β-Phenoxy acids can be prepared in two known ways. In one, which is applicable to phenoxyaliphatic acids in general, the phenoxide is treated with a halo ester, nitrile, and so forth, the chlorine being separated from the other functional group by the aliphatic chain. An instance is the use of β-chloropropionitrile; the phenoxy nitrile is subsequently hydrolyzed. The alternative procedure is appli-



cable only to α,β-unsaturated esters, nitriles, and so forth; a trace of alkali catalyzes the addition of a phenol to the carbon-carbon double bond of the unsaturated component.



Various other preparations are mentioned in the literature. A novel method for producing α-phenoxybutyric acid is given by Bentley, Haworth, and Perkin (6). α-Phenoxyethylmalonic acid is heated to 150°-160°C. and then treated with ether to extract the α-phenoxybutyric acid. This acid was prepared by Nair and Peacock (7) by a different method. α-Phenoxyethyl *p*-toluenesulfonate was treated with sodium ethoxide and acetoacetic ester, followed by potassium hydroxide and ethyl alcohol. Aside from these special preparations, phenoxybutyric acid is generally prepared through the nitrile, ester, or amide.

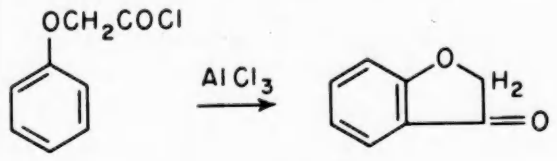
Reactions

Phenoxy acids are *ortho-para* directors on nuclear substitution. The *para*-position is the first position attacked. The nucleus may be halogenated, but nitro derivatives are not obtained by direct nitration, but by the usual method of condensing the nitrophenol with the chloro acid. Monohalogenation proceeds readily at room temperature. Disubstitution occurs only at higher temperatures. Many chemists prefer nuclear halogenation to using the substituted phenol condensation type of reaction. It is maintained that the reaction is more easily controlled and the products are better defined. Monochlorination proceeds at room temperature, dichlorination in the 2,4-positions occurs at 60°-80°C., and trichlorination follows above this temperature range, giving the 2,4,6-trichloro derivative. Sulfuryl chloride, phosphorus pentachloride, as well as chlorine gas, are used.

Nitrophenoxy acids can be reduced to the corresponding amino derivatives by any of several methods. The best and currently most popular method of reduction involves the use of ferrous sulfate and ammonium hydroxide (3). The ammonium salt thus formed is treated with excess acetic acid and heated to yield the corresponding aminophenoxy acid. Another method of reduction utilizes tin and hydrochloric acid. This method has become less prominent because of the difficulty of removing

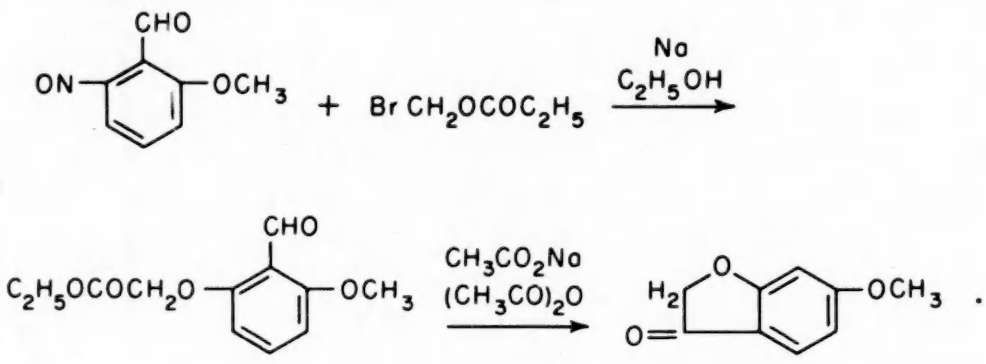
the tin salts from the reaction mixture. Hydrogen sulfide can be used to precipitate the tin, but this is a tedious and time-consuming process. This reduction is of particular interest to the dye chemist, since aminophenoxy acids are readily diazotized and coupled.

Phenoxy acids undergo cyclization to chromanones and coumaranones. 3-Coumaranone can be prepared by the cyclization of phenoxyacetyl chloride, with aluminum chloride as a catalyst (8). The attempted cyclization of 2,4-dichlorophenoxyacetic

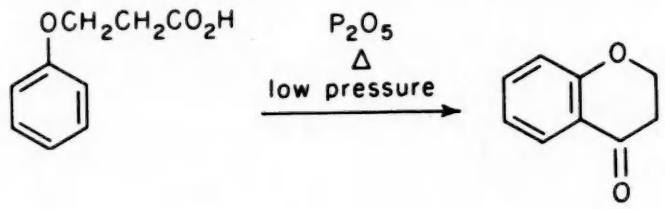


acid with phosphorus pentoxide results in fragmentation (9). The product obtained is 2,4-dichlorophenyl-2,4-dichlorophenoxy acetate. Evidently, the ether linkage cleavage is stimulated by the phosphorus pentoxide, followed by esterification of the 2,4-dichlorophenoxyacetic acid by the phenol fragment.

6-Methoxycoumaran-3-one is prepared as follows:

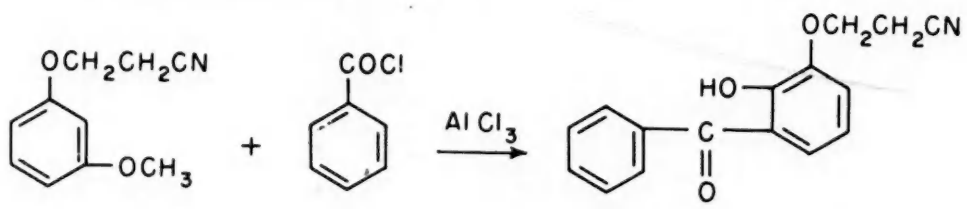


A ring closure using β-phenoxypropionic acid with phosphorus pentoxide results in the formation of chromanone (10). 6-Methylchromanone can be made in the same



manner, starting with β-(*p*-toloxy)propionic acid.

Phenoxycarboxylic acids undergo Friedel-Crafts acylation, as exemplified by the reaction of β-(*m*-methoxyphenoxy)propionitrile with benzoyl chloride in the presence of aluminum chloride, followed by hydrolysis of the nitrile to give the acid (11). How-



ever, if the corresponding ethyl ester of phenoxypropionic acid is treated in the same manner, the results are quite different. The resulting material is composed of carboxylic, phenolic, and neutral fragments.

Phenoxyacetic acid, when reacted with *p*-hydroxybenzaldehyde in the presence of trimethylamine and acetic anhydride, gives α-phenoxy-*p*-hydroxycinnamic acid (12).

Another special reaction is shown by heating 3-methoxyphenoxyacetic acid, ethyl ester, with potassium cyanide and ammonium carbonate under a pressure of 20 atmospheres of carbon dioxide to give the ethyl ester of 5-(3-methoxyphenoxymethyl)hydantoin-5-acetic acid (13).

Uses

The most widely recognized uses of phenoxycarboxylic acids are those pertaining to plant-growth activity. Many derivatives of these acids are active plant hormones. Some react to retard plant growth and others tend to stimulate it. In a thorough study of the control of plant growth, it was found that when the *ortho*-position of the substituted phenoxyacetic acid is blocked, growth is markedly decreased (14). The conclusion was reached that these phenoxyacetic acids react through the *ortho*-position with a plant substrate. If the *ortho*-position is not occupied, growth is enhanced. The chemical reaction of a plant substrate is of greater importance than absorbability for the manifestation of plant-growth regulation.

Investigation has shown that: (a) halogen or methyl groups in phenoxy acids are the most important in effecting activity for plant-cell elongation; (b) the halogen derivatives appear to influence growth more than the methyl; and (c) the 2-, 3-, and 4-positions exert the greatest influence.

Recently, it was found that an exchange resin made from phenoxyacetic acid with formaldehyde and sulfuric acid was of value in the separation of amino acids and in the exchange of sodium–calcium and of other metallic ions. In the field of plastics, certain polyglycol esters of phenoxy acetic acid were found to plasticize cellulose acetate (15). The fact that most of the derivatives of phenoxyacetic acid are easily identifiable solids led to their use to identify substituted phenols (16). The derivatives are, for the most part, easily prepared and purified, and provide a convenient method of organic qualitative analysis.

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